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On: April 4, 2002

TOWNSEND and TOWNSEND and CREW LLP

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PATENT
Attorney Docket No.: 15270J-004761US
Client Ref. No.: 209-US-CIP8BC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: S. Turner
DALE B. SCHENK et al.	Art Unit: 1647
Application No.: 09/724,552	COMMUNICATION UNDER 37 C.F.R. §§ 1.821-1.825
Filed: November 28, 2000	AND
For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE	REQUEST TO REFERENCE PREVIOUSLY FILED IDENTICAL COMPUTER READABLE COPY ACCORDING TO 37 CFR 1.821(e)
	AND
	PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This Communication Under 37 CFR 1.821-825; Preliminary Amendment; and, Request to Reference Previously Filed Identical Computer Readable Copy According to 37 CFR 1.821(e) is submitted in response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed March 22, 2002. Applicants respectfully request that the specification be amended in adherence with 37 C.F.R. §§ 1.821-1.825 as follows.

Please insert the paper copy of the Sequence Listing (pages 1-22), submitted herewith, at the end of the application.

Please replace the paragraph beginning at page 7, line 32, with the following replacement paragraph:

Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

Please replace the paragraph beginning at page 8, line 5, with the following replacement paragraph:

Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

Please replace the paragraph beginning at page 14, line 13, with the following replacement paragraph:

H_2N-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH (SEQ ID NO:42).

Please replace the paragraph beginning at page 28, line 14, with the following replacement paragraph:

Some agents for inducing an immune response contain the appropriate epitope for inducing an immune response against amyloid deposits but are too small to be immunogenic. In this situation, a peptide immunogen can be linked to a suitable carrier to help elicit an immune response. Suitable carriers include serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, or a toxoid from other pathogenic bacteria, such as diphtheria, *E. coli*, cholera, or *H. pylori*, or an

attenuated toxin derivative. Other carriers include T-cell epitopes that bind to multiple MHC alleles, e.g., at least 75% of all human MHC alleles. Such carriers are sometimes known in the art as "universal T-cell epitopes." Examples of universal T-cell epitopes include:

Influenza Hemagluttinin: $HA_{307-319}$ PKYVKQNTLKLAT (SEQ ID NO:43)

PADRE (common residues bolded) AKXVAAWTLKAAA (SEQ ID NO:44)

Malaria CS: T3 epitope EKKIAKMEKASSVFNV (SEQ ID NO:45)

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Hepatitis B surface antigen: $HBsAg_{19-28}$ FFLLTRILTI (SEQ ID NO:46)

Heat Shock Protein 65: $hsp65_{153-171}$ DQSIGDLIAEAMDKVGNEG (SEQ ID NO:47)

bacille Calmette-Guerin QVHFQPLPPAVVKL (SEQ ID NO:48)

Tetanus toxoid: $TT_{830-844}$ QYIKANSKFIGITEL (SEQ ID NO:49)

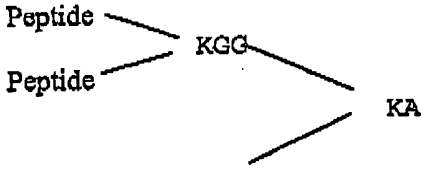
Tetanus toxoid: $TT_{947-967}$ FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:50)

HIV gp120 T1: KQIINMWQEVGKAMYA (SEQ ID NO:51).

Please replace the paragraph beginning at page 30, line 24, with the following replacement paragraph:

B5

The MAP4 configuration is shown below, where branched structures are produced by initiating peptide synthesis at both the N terminal and side chain amines of lysine. Depending upon the number of times lysine is incorporated into the sequence and allowed to branch, the resulting structure will present multiple N termini. In this example, four identical N termini have been produced on the branched lysine-containing core. Such multiplicity greatly enhances the responsiveness of cognate B cells.



Peptide
KGG
Peptide

AN90549 (Aβ 1-7/Tetanus toxoid 830-844 in a MAP4 configuration):

DAEFRHDQYIKANSKFIGITEL (SEQ ID NO:52)

AN90550 (Aβ 1-7/Tetanus toxoid 947-967 in a MAP4 configuration):

DAEFRHDFNNFTVSFWLRVPKVSASHLE (SEQ ID NO:53)

AN90542 (Aβ 1-7/Tetanus toxoid 830-844 + 947-967 in a linear configuration):

DAEFRHDQYIKANSKFIGITELFNNFTVSFWLRVPKVSASHLE

(SEQ ID NO:54)

AN90576: (Aβ 3-9)/Tetanus toxoid 830-844 in a MAP4 configuration):

EFRHDSGQYIKANSKFIGITEL (SEQ ID NO:55)

B5

Peptide described in US 5,736,142 (all in linear configurations):

AN90562 (Aβ 1-7/ peptide) AKXVAAWTLKAAADAEFRHD (SEQ ID NO:56)

AN90543 (Aβ1-7 x 3/ peptide): DAEFRHDDAEFRHDDAEFRHDAKXVAAWTLKAAA

(SEQ ID NO:57)

Other examples of fusion proteins (immunogenic epitope of Aβ bolded) include

AKXVAAWTLKAAA-**DAEFRHD-DAEFRHD-DAEFRHD**

(SEQ ID NO:58)

DAEFRHD-AKXVAAWTLKAAA (SEQ ID NO:59)

DAEFRHD-ISQAVHAAHAEINEAGR (SEQ ID NO:60)

FRHDSGY-ISQAVHAAHAEINEAGR (SEQ ID NO:61)

EFRHDSG-ISQAVHAAHAEINEAGR (SEQ ID NO:62)

PKYVKQNTLKLAT-**DAEFRHD-DAEFRHD-DAEFRHD**

(SEQ ID NO:63)

DAEFRHD-PKYVKQNTLKLAT-**DAEFRHD** (SEQ ID NO:64

DAEFRHD-DAEFRHD-DAEFRHD-PKYVKQNTLKLAT

(SEQ ID NO:65)

DAEFRHD-DAEFRHD-PKYVKQNTLKLAT (SEQ ID NO:66)

DAEFRHD-PKYVKQNTLKLAT-EKKIAKMEKASSVFNV-
QYIKANSKFIGITEL-FNNFTVSFWLRVPKVSASHLE-**DAEFRHD**

(SEQ ID NO:67)

DAEFRHD-DAEFRHD-DAEFRHD-QYIKANSKFIGITEL-
FNNFTVSFWLRVPKVSASHLE (SEQ ID NO:68)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE

(SEQ ID NO:69)

B5 **DAEFRHD**-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE-
DAEFRHD (SEQ ID NO:70)

DAEFRHD-QYIKANSKFIGITEL on a 2 branched resin

(SEQ ID NO:77)

peptide
Lys-Gly-Cys
peptide

EQVTNVGGAISQAVHAAHAEINEAGR (SEQ ID NO:71) (Synuclein fusion protein in MAP-4 configuration).

Please replace the paragraph beginning at page 60, line 24, with the following replacement paragraph:

B6 Preparation of coupled Aβ peptides: four human Aβ peptide conjugates (amino acid residues 1-5, 1-12, 13-28, and 33-42, each conjugated to sheep anti-mouse IgG) were prepared by coupling through an artificial cysteine added to the Aβ peptide using the

crosslinking reagent sulfo-EMCS. The Aβ peptide derivatives were synthesized with the following final amino acid sequences. In each case, the location of the inserted cysteine residue is indicated by underlining. The Aβ13-28 peptide derivative also had two glycine residues added prior to the carboxyl terminal cysteine as indicated.

B6

Aβ1-12 peptide	NH2-DAEFRHDSGYEVC-COOH (SEQ ID NO:72)
Aβ1-5 peptide	NH2-DAEFRC-COOH (SEQ ID NO:73)
Aβ33-42 peptide	NH2-C-amino-heptanoic acid-GLMVGGVVIA-COOH (SEQ ID NO:74)
Aβ13-28 peptide	Ac-NH-HHQKLVFFAEDVGSNKGGC-COOH (SEQ ID NO:75)

Please replace the paragraph beginning at page 102, line 8, with the following replacement paragraph:

B7

The exact array of linear peptides recognized by the antibodies in the serum samples from animals immunized with AN1792 was determined by an ELISA that measured the binding of these antibodies to overlapping peptides that covered the entire Aβ1-42 sequence. Biotinylated peptides with partial sequences of AN1792 were obtained from Chiron Technologies as 10 amino acid peptides with an overlap of 9 residues and a step of one residue per peptide (synthesis No. 5366, No. 5331 and No. 5814). The first 32 peptides (from the eight amino acid position upstream of the N-terminal of AN1792 down to the twenty-fourth amino acid of AN1792) are biotinylated on the C-terminal with a linker of GGK. The last 10 peptides (repeating the thirty-second peptide from the previous series) are biotinylated on the N-terminal with a linker consisting of EGEG (SEQ ID NO:76). The lyophilized biotinylated peptides were dissolved at a concentration of 5 mM in DMSO. These peptide stocks were diluted to 5 μM in TTBS (0.05% Tween 20, 25 mM Tris HCl, 137 mM NaCl, 5.1 mM KCl, pH=7.5). 100 μl aliquots of this 5 μM solution were added in duplicate to streptavidin pre-coated 96-well plates (Pierce). Plates were incubated for one